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Review

# Glucocerebrosidase and Parkinson disease: Recent advances

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ABSTRACT

Mutations of the glucocerebrosidase (GBA) gene are the most important risk factor yet discovered for Parkinson disease (PD). Homozygous GBA mutations result in Gaucher disease (GD), a lysosomal storage disorder. Heterozygous mutations have not until recently been thought to be associated with any pathological process. However, it is clear that the presence of a GBA mutation in homozygous or heterozygous form is associated with an approximately 20-fold increase in the risk for PD, with little if any difference in risk burden related to gene dose. Most studies suggest that 5–10% of PD patients have GBA mutations, although this figure is greater in the Ashkenazi population and may be an underestimate overall if the entire exome is not sequenced. GBA-associated PD is clinically indistinguishable from idiopathic PD, except for slightly earlier age of onset and a greater frequency of cognitive impairment. Pathological and imaging features, and response to pharmacotherapy are identical to idiopathic PD. GBA mutations result in reduced enzyme activity and mutant protein may become trapped in the endoplasmic reticulum (ER) leading to unfolded protein response and ER associated degradation and stress. Both mechanisms may be relevant in GD and PD pathogenesis and lead to impaired lysosomal function. Of particular relevance to PD is the interaction of glucocerebrosidase enzyme (GCase) with alpha-synuclein (SNCA). There appears to be a bi-directional reciprocal relationship between GCase levels and those of SNCA. Thus reduced GCase in GBA mutation PD brain is associated with increased SNCA, and increased SNCA deposition is associated with reduced GCase even in GBA wild-type PD brains. It is noteworthy that GBA mutations are also associated with an increase in risk for dementia with Lewy bodies, another synucleinopathy. It has been suggested that the relationship between GCase and SNCA may be leveraged to reduce SNCA levels in PD by enhancing GCase levels and activity. This hypothesis has been confirmed in GBA mutant mice, PD patient fibroblasts and cells with SNCA overexpression, and offers an important target pathway for future neuroprotection therapy in PD. This article is part of a Special Issue entitled 'Neuronal Protein'.



**Contents**



## 1. Introduction

Parkinson disease (PD) is a multicentric neurodegenerative disease characterised pathologically by the loss of dopaminergic neurons in the substantia nigra pars compacta and other brain stem nuclei, as well as by the presence of alpha-synuclein (SNCA) aggregates in Lewy bodies and neurites. The aetiology and pathogenesis of PD have been the subject of much research for over more than a century, in the hope that this might lead to effective treatments. In part, this ambition has been achieved with the identification of dopamine deficiency in PD brain and the improvement of symptoms with the use of dopaminergic drugs. However, this strategy has limitations in terms of its effectiveness – not all PD symptoms are caused by dopamine deficiency – and a side effect profile that includes levodopa related motor complications. The most important challenge is to develop therapies that

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can prevent, slow or reverse the neurodegeneration associated with PD. For this, a clear understanding of the causes and biochemical pathways leading to PD needs to be defined.

There have been substantial advances in our understanding of the genetic factors associated with PD, and of the abnormal biochemistry of the PD brain (Schapira and Jenner, 2011). The accumulation of SNCA has been considered central to the pathogenesis of PD, as reflected by mutations, multiplications and polymorphisms of the *SNCA* gene that lead to abnormal protein, an increased generation or accumulation of wild-type protein and which are associated with PD (Lin and Farrer, 2014). Although several gene mutations have been described in familial PD, taken together these still remain relatively rare, accounting for probably <10% of all cases (Mullin and Schapira, 2015). Genome-wide association studies in PD have demonstrated a number of additional significant genetic associations with PD, confirming SNCA and tau, but adding components of the immune cascade (Nalls et al., 2014). Probably the most exciting of all genetic associations with PD is the identification that mutations of the glucocerebrosidase gene (GBA1) are a significant risk factor for the disease. This relationship was first identified in the Ashkenazi Jewish population and began to attract attention after a number of reports (Aharon-Peretz et al., 2004; Tayebi et al., 2001). This review seeks to provide an update on certain aspects of the glucocerebrosidase link with PD and the potential for the development of future therapies to target this area.

## 2. Genetics

The lysosomal enzyme glucocerebrosidase (GCase) is encoded by the *GBA1* gene on chromosome 1q21. It has 11 exons, 10 introns and is 7.6 kb in total with a nearby 5.6 kb pseudogene, 16 kb downstream (Horowitz et al., 1989). GCase metabolises glucocerebroside to glucose and ceramide and mutations of *GBA1* cause the autosomal recessive lysosomal storage disorder Gaucher disease (Grabowski, 2008). Over 300 different mutations of the *GBA1* gene have been described, but the N370S and L444P account for the majority of those found in both Gaucher disease and PD. Gaucher disease has an estimated frequency of 1:50,000 live births, but this rises to 1:850 in the Ashkenazi Jewish population. Both Gaucher patients and asymptomatic heterozygous gene carriers are recognised to be at almost equal risk of PD. The penetrance and lifetime risk of developing PD for those with a *GBA1* mutation varies with some figures quoting up to 20% at 70 years and 30% at 80 years (Beavan and Schapira, 2013). The proportion of PD patients that carry *GBA1* mutations is estimated to be between 5 and 10%, but this range may be an underestimate in some populations and also depends on whether the entire exome has been sequenced (Kumar et al., 2013; Lesage et al., 2011; McNeill et al., 2012a; Neumann et al., 2009; Sidransky et al., 2009). Certain *GBA1* sequence variants e.g., E326K have been associated with PD and not Gaucher disease and this further increases the proportion of PD patients that are associated with *GBA1* mutations (Duran et al., 2013). The proportion of PD cases that carry *GBA1* mutations in Japan appears to be similar with 9.4% of PD cases carrying *GBA1* mutations with an odds ratio of 28 compared to controls (Mitsui et al., 2009). In the Chinese PD population, 3.72% of cases had *GBA1* mutations, with an odds ratio of 15 compared to controls (Huang et al., 2011).

Thus, *GBA1* mutations represent the most important risk factor for PD identified to date. These mutations are substantially more common than other PD associated genes such as *LRRK2* or *SNCA*. GBA1 has also been associated with dementia with Lewy bodies, strengthening its relationship to SNCA pathology (Goker-Alpan et al., 2006; Mata et al., 2008; Nalls et al., 2013). *GBA1* mutations have not been found at increased frequency in multiple system atrophy, progressive supranuclear palsy or corticobasal degeneration (Jamrozik et al., 2010; Segarane et al., 2009; Srulijes et al., 2013).

## 3. Clinicopathological correlates

Individual PD patients with *GBA1* mutations cannot be discriminated from idiopathic PD without *GBA1* mutations on clinical or pathological grounds. There are some interesting clinical features when the PD-GBA1 group is taken as a whole. For instance, PD-GBA1 patients exhibit the classic triad of bradykinesia, rigidity and tremor, with asymmetric onset (Goker-Alpan et al., 2008). However, age of onset tends to be slightly younger and there is a greater risk for earlier and more prevalent cognitive impairment in PD-GBA1 patients (Sidransky et al., 2009; Winder-Rhodes et al., 2013). The pattern of cognitive dysfunction in *GBA1* positive carriers was slightly different and present in those even without PD at the time of investigation (Zokaei et al., 2014). In contrast to other genetic causes of PD, imaging with fluorodopa positron emission tomography or single photon emission tomography with dopamine sensitive ligands in PD-GBA1 demonstrate an asymmetric pattern of abnormality indistinguishable from idiopathic PD (Goker-Alpan et al., 2012; McNeill et al., 2013b). Patients with GBA1 mutations also exhibit greater retinal abnormalities in terms of thickness as determined by optical coherence tomography compared to matched PD patients (McNeill et al., 2013a).

Of particular interest is the evidence accumulating that *GBA1* mutant homozygote and heterozygote carriers without clinical evidence of PD, exhibit the prodromal features of the disease. Olfactory function and cognitive assessment were significantly reduced, and motor testing abnormal in *GBA1* positive cases compared to controls (McNeill et al., 2012b). A two year follow-up showed significant deterioration in scores for depression, rapid eye movement sleep behaviour disorder, cognition, olfaction and motor scores (Beavan et al., 2015). These data indicate that individuals with *GBA1* mutations exhibit identical prodromal abnormalities to those with idiopathic PD. There appears to be a relatively rapid evolution of non-motor and motor features in this cohort. Further follow up of this group will enable early diagnosis in those progressing to clinical PD and perhaps allow identification of a specific clinical or biochemical pattern that distinguishes those with *GBA1* mutations who will and those who will not develop PD.

The pathology of *GBA*1 mutation positive PD appears to be identical to that of idiopathic disease. In a retrospective analysis of brains exhibiting the characteristic pathology of PD, *GBA1* mutations were found in almost 5% (Neumann et al., 2009; Wong et al., 2004). GCase has also been found in Lewy bodies, more frequently in those with *GBA1* mutations (Goker-Alpan et al., 2010). Some studies have suggested that Lewy body deposition is more extensive in GBA1 mutant positive brains (Clark et al., 2009) but this is not universally found (Parkkinen et al., 2011).

The response to dopaminergic therapy in PD-GBA1 appears to be the same as that seen in idiopathic PD, including the development of motor complications (Ziegler et al., 2007). In one centre, retrospective genetic analysis identified *GBA1* mutations in 17% of those who had undergone deep brain stimulation, and in whom clinical effect was as good as those without mutations (Angeli et al., 2013).

## 4. Biochemistry

The presence of a *GBA1* mutation is invariably associated with a reduction in GCase enzyme activity, although the degree of this varies between mutations. Homozygous Gaucher patients may have <1% residual activity, while heterozygous carriers may have 50–60% residual activity, depending on the mutation. Peripheral GCase activity from fibroblasts has been recently studied in samples from PD patients with and without *GBA1* mutations, and in Gaucher patients with various *GBA1* mutations (McNeill et al., 2014). However, the mechanism by which *GBA1* mutations increase the risk for PD may operate through additional or alternative mechanisms than simply GCase deficiency, and this is discussed below.

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